学位論文の要旨

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学位論文名	Changes of Noradrenaline-Induced Contractility and Gene Expression in Aorta of Rats Acclimated to Heat in Two Different Modes
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論文内容の要旨

INTRODUCTION

Acclimation to heat has been shown to bring about various changes in thermoregulatory function to neutralize a rise in core temperature in hot conditions in animals. One of the characteristic events is an enhancement of nonevaporative heat loss response, i.e. a skin blood flow response, to heat stress. The enhanced skin blood flow is achieved by various factors, such as augmented dilator responses of arteries directly supplying blood to the skin and increases in compliance of conduit arteries. Recently, we have shown that in humans, compliance of arteries in the extremities could be improved after acclimation to heat. However, the evidence in humans was limited since the methods for estimating compliance were based on a theoretical model. Thus, the first objective of this study was to assess in heat-acclimated rats reactivity of arteries to a physiological modulator, noradrenaline (NA).

It has been shown that a time memory could be formed by timed daily heat exposure, e.g. venous and arterial compliance of humans acclimated to heat given for 4 h in the afternoon was reported to increase only during the period when the subjects were previously exposed to heat. The second objective was then to examine how the timed daily heat exposure affected the pattern of nycthemeral variations in arterial function in rats.

Vascular distensibility is modified by endothelium-derived relaxing factors, such as nitric oxide (NO) and adenyl purines (APUs). Thus, we also investigated effects of heat acclimation on endothelial and inducible NO synthase (eNOS and iNOS) mRNA

expressions and the capacity of adenyl purine release in the arteries. In addition, plasma nitrite/nitrate (NOx) levels were examined.

MATERIALS AND METHODS

Male Wistar rats were divided into 3 groups; the control group (CN) and two types of heat-acclimated groups (HI and HC). CN was maintained at 24℃. For HI, rats were exposed to 32℃ only during the last half of the dark phase. HC was constantly kept at 32℃. The heat exposure was repeated for 10 consecutive days. Then, each rat was anesthetized in the first (Dark1) or second (Dark2) half of the dark phase, or in the light phase (Light), and the thoracic aorta, caudal artery and/or femoral artery were removed.

The arterial segments were mounted in an organ bath. Concentration-response curves to accumulative NA (10^{-10}~10^{-5} M) were obtained. The values of NA-induced contraction were expressed as a percentage of maximal contraction induced by KCl. The other arterial samples were stimulated with 1 μM of NA for 3 min and the bathing solutions were collected. The amounts of ATP, ADP, AMP and adenosine in samples were determined by HPLC with fluorescence detector. Total RNA was extracted from aorta and tail artery, and cDNA was synthesized. Real-time PCR were carried out using a quantitect SYBR green PCR kit with gene specific primers (eNOS, iNOS, Per2 and β-actin). The concentrations of plsama NOx (NO^{2-} and NO^{3-}) were determined using a Nitric Oxide Quantitation Kit.

Results are expressed as means ± SEM. Data for concentration-response curves to NA were analyzed by repeated measures of two-way (group and concentration) analysis of variance (ANOVA). The other data were evaluated by oneway (group) ANOVA at each phase of the day. ANOVA was followed by Fisher's Protected Least Significant Difference test for post hoc comparisons. A level of $p<0.05$ was considered significant.

RESULTS AND DISCUSSION

In thoracic aorta, the contraction response to NA in HI was significantly depressed in Dark 1 and Dark 2, whereas in HC the contraction response was significantly attenuated in all phases. In caudal and femoral arteries, the contraction response to NA did not differ among groups at any phases. The amounts of APUs released by NA in aorta and caudal artery were not affected by heat acclimation. Heat acclimation had no effect on aortic eNOS mRNA expressions in Dark1 and Light. In Dark2, however, the level of HI was significantly higher than that of CN and HC. In caudal artery, the level of eNOS mRNA expression was not affected by heat acclimation. iNOS mRNA was undetectable. Plasma NOx concentration in HI was significantly elevated in Dark 1 and Dark 2. In HC, the NOx level was consistently elevated in all phases.

The present study showed that in rats, heat acclimation attenuated contractile responses to NA in thoracic aorta, and suggest that at a given level of sympathetic nervous tone, compliance of aorta was increased in heat-acclimated animals. However, the 10-day heat exposure had a minimum impact on function in crucial acral vessels for

heat dissipation. The aorta is a dynamic organ, capable of instantaneous changes in size, and plays an important role in regulating left ventricular performance and interaction of the entire cardiovascular system. The attenuated contractility of thoracic aorta may be one of preferable cardiovascular adjustments in heat-acclimated rats to resist to heat.

The present study has also confirmed that changes in aortic function of heat-acclimated rats depend on the mode of the heat exposure schedule to attain heat acclimation. In HI, which was subjected to heat in the second half of the dark phase, the attenuated contractile responses of aorta to NA were clearly observed in the dark phase of the day, whereas in HC exposed to heat throughout a day, the depressed vasoconstrictor responses were observed in all tested phases of the day. Thus, it appears that in rats, the time of the day when heat acclimation-induced changes in aortic vasocontractility occurs is closely related to the time when rats were previously exposed to heat.

In HI, eNOS mRNA expression in aorta was significantly increased in Dark2 when the contractile response to NA was significantly blunted. Although the eNOS mRNA level does not directly reflect the amount of NO released from endothelium, this observation may be suggestive of the involvement of eNOS induction and NO production in attenuation of aortic contraction response to NA in HI. However, since in HC and in Dark1 in HI, NA-induced vasoconstriction was depressed without an associated rise in eNOS mRNA expression, NO released from endothelium may not be a indispensable factor to modify aortic function. Nevertheless, there are two noteworthy findings in the present study, i.e. heat acclimation could upregulate eNOS mRNA expression in aorta in HI, enhanced eNOS mRNA expression was specifically seen during the period when rats had been previously exposed to heat.

CONCLUSION

Our study showed that heat acclimation attenuated contractile responses to NA and augmented eNOS mRNA expression in aorta, and elevated plasma NOx levels. These functional changes depended on the mode of heat exposure schedule, i.e. alterations were seen around the period when the animals had been previously exposed to heat. Heat acclimation had minimum influence on vasomotor function in caudal artery, an important vessel to dissipate heat.